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Editorial

Rhinoconjunctivitis and wheeze in preschool children: a different relationship than in adults (United or Coexistent Airways Disease)?

G. Viegi[1], S. La Grutta[2]

[1]Unità di Epidemiologia Ambientale Polmonare, Istituto di Fisiologia Clinica CNR, Pisa; [2]Unità di Ambiente e Salute, Agenzia Regionale di Protezione Ambientale della Sicilia ed Istituto di Biomedicina ed Immunologica Molecolave 'A. Monroy' CNR, Palermo, Italy

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Giovanni Viegi
CNR Institute of Clinical Physiology–Pulmonary Environmental Epidemiology Unit
Via Trieste
41-56126 Pisa
Italy

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In the last years the evidence of an association between rhinitis and asthma has been growing (1). Indeed, Passalacqua et al. (2) used the term of United Airways Disease (UAD) to indicate a continuum in the pathological processes affecting upper and lower airways.

However, signs of diverging trends in the epidemiology of rhinitis and asthma have recently been brought to our attention. Von Hertzen and Haahtela (3), in a recent review on Allergy, pointed out that data on stable or decreasing trends in prevalence of asthma were reported by 13 studies and on continuously increasing trends in prevalence of asthma by nine studies, whilst disparities in trends for asthma and allergic rhinitis were observed by three studies.

In Italy, Galassi et al. (4), in one of the largest national contributions to the International Study of Asthma and Allergies in Childhood (ISAAC), have demonstrated an increasing trend for both rhinitis and asthma in 6- to 7-years-old children, whereas in 12- to 13-years-old adolescents frequencies of asthma decreased and of rhinitis increased in 2002 with respect to 1994.

The pattern has become more complex with the recent publication of the global ISAAC data (5) depicting a scenario in which all the three possibilities (increasing, decreasing or steady trend) are present in the various regions of the world. With regard to the 12 month prevalence of allergic rhinoconjunctivitis, the ISAAC data exhibit a wide range (from 2.2% in Iran to 24.2% in Taiwan), with UK showing the highest value (10.1%) for Western Europe.

In addition, it had been reported that the proportion of rhinitis cases attributable to atopy is 53% with little evidence of systematic geographic variation in population-based studies (6).

The merit of Marinho et al. (7), who report in this issue of *Allergy* on the Manchester Asthma and Allergy Study (MAAS), is to have added data referring to preschool children, for whom the pattern of association between the two diseases and among rhinoconjunctivitis and risk factors may differ from those in older children or in adults.

They studied a relatively small population sample of 5-years-old children, but with the advantage of being a whole-population birth cohort in a UK city.

They confirmed the elevated frequency of rhinitis (one out of four individuals) and of current rhinoconjunctivitis (CRC) (one out of eight) in UK children, as well as the coexistence of CRC with asthma, wheeze and eczema.

However, they found less numerous associations with risk factors (family history of allergic disease and sensitization to inhalant allergens) than those expected, and small differences in risk factors between atopic and nonatopic CRC. Furthermore, they failed to show any link with severity of wheeze, increased airway reactivity and reduced lung function.

One important item of discussion is the correctness of the diagnosis of CRC achievable in epidemiological surveys. One has to consider that, for diagnosing allergic diseases, the gold standard is the positive skin test, especially for inhalant allergens (8). Marinho et al. used a validated questionnaire (the ISAAC one) (9), which, however, has been shown as highly specific but poorly sensitive when compared with skin prick test (10).

In the questions of nose and eyes disturbances there is no mention of other symptoms/signs which might be present in such inflammatory conditions, such as redness and ache. Further, the huge discordance between the frequency of rhinitis ever (28.2%) and the doctor-diagnosed allergic rhinitis/hay fever (5.3%) seems to indicate that parents seldom tend to ask the advice of a doctor, which, in turn, probably makes the diagnosis in the most severe cases only. Recently, objective tests such as acoustic rhinometry (11) and tear film break-up time, blink frequency or cells/inflammatory markers in tear fluid (12) have usefully been applied in epidemiology. It is auspicial that in the future such tests may be more easily used in clinical practice and help to refine the validity of the questionnaire.

Alternatively, the use of a questionnaire able to give a quantitative dimension of RC through a score (13) might help studying the natural history of RC by examining possible linear relationships with lung function tests or dose-response relationships with risk factors.

Indeed, Marinho et al. (7) confirmed the coexistence of CRC with current wheeze: 38.8% of CRC children also reported wheeze, whilst 24.7% of wheezy children also reported CRC. Higher frequencies of reported comorbidity, as well as functional, immunological and therapeutic considerations, had induced Passalacqua et al. (2) to refer the nose-lung interaction in allergic rhinitis and asthma as UAD. However, Marinho et al. (7) reported no modifying effect of CRC on either severity or frequency of wheezy episodes. Thus, it seems that, although coexistent, the two airway disorders are less inter-related than in older children or in adults, suggesting that in preschool children we might rather use the term of CAD (Coexistent Airway Diseases) instead of UAD.

Marinho et al. (7) also confirmed that there is a strong genetic component in CRC as evidenced by the two- to threefold increase in risk associated with parental allergic diseases strengthening that the atopic phenotype in early childhood is an expression of heritable factors, allergens and synergy with other environmental triggers.

Conversely, they did not find associations with male gender, position in sibship, day care attendance, immunization, duration of breastfeeding, pet exposure, environmental tobacco exposure, endotoxin exposure.

For many of these factors, this is not surprising as the results in the literature are controversial and show the difficulty of studying the effect of risk factors through questionnaires in different populations.

It is to point out that the adoption of different lifestyle by families of atopic children, depending on whether atopic manifestations are present in parents, may increase the occurrence of selection and information biases in epidemiological studies on the aetiology of allergy in children (14). Similarly, when parents are atopic, infants' pets are less often present in families with parental atopy (15).

The lack of association with symptoms and signs of airflow obstruction opens the question on the relevance of wheeze (in terms of frequency and severity) and airway functional tests in the screening approach to rhinitis symptoms in childhood. Indeed, previous data in a smaller group of well characterized allergic rhinitis children indicated a strong association between bronchial hyper-responsiveness (BHR) and atopic rhinitis (16, 17).

As Marinho et al. (7) suggest, the follow-up observation is a good way for detecting the lower airway involvement, mainly the relationship between BHR and asthma development, and for monitoring the progression of allergic disease.

The finding of allergic symptoms without allergic sensitization is also debatable, in view of some results from cohort studies, in which the crucial role of early allergic sensitization to perennial allergens (e.g. house dust mite, cat and dog hair), associated with a loss of lung function at school age, has been shown (18).

The results about the sensitizations to grass and cat allergens as significant and independent risk factors associated with CRC confirm previous data about the role of sensitization to cat allergen as an important risk factor for childhood asthma (19, 20).

Furthermore, Marinho and colleagues do not support the evidence of a role of mite and pet exposure for allergic disease in young children according to a recent systematic review in which the harmful effect of pet exposure for wheezing appears in children over 6 years, but not in the younger ones (21).

As regards mite exposure, there is conflicting evidence about the relationship between house dust mite (HDM) levels and sensitization and about the inconsistency of HDM avoidance measures on sensitization (22). This leads the authors to raise the question of the opportunity and time-dependent application of prevention measures. They also stress the concept that the early recognition of these young children with rhinoconjunctivitis should be considered as an ideal target for the secondary prevention. Although not quoted herein, it is worthwhile to cite a therapeutic intervention that might interfere with the natural course of allergic diseases in young atopic

children, i.e. the Specific Immunotherapy (23–25), for which long term follow-up studies might also provide important pieces of knowledge.

Likewise, the lack of effect of environmental tobacco smoke may be related to a reduced exposure than in the past, as provided by both a lower prevalence of smoking parents and a more protecting behaviour of conscious parents.

The breast feeding duration is a frequently debated issue, regarding the association with allergic disease in children without and with an allergic predisposition. Some results suggest that this protective effect is found in children with or without a family history of atopy (26, 27), especially on the early development of multiple allergic diseases, such as asthma, atopic dermatitis and suspected allergic rhinitis (28). Conversely, a protective effect of prolonged breastfeeding on allergic disease, particularly hay fever, only in children without allergic parents, has been reported (29).

Again, the cohort studies in which several time dependent information on the same subject are collected prospectively and the use of biomonitors should provide additional information that hopefully will clarify this issue.

At last, it is to point out that other variables, not mentioned in the MAAS, might affect CRC. One is mould/dampness exposure, especially in the first year of life, as reported by Simoni et al. (30), who found that up to 4% of rhinoconjunctivitis is attributable in children to such an indoor exposure.

Another potentially important variable is outdoor air pollution, as shown by Bayer-Oglesby et al. (31) who reported decreased prevalence rates of conjunctivitis (−23%) and sneezing (−18.8%) after reduction of air pollution concentrations in the SCARPOL study. Furthermore, Johnson and Graham (32) estimated that up to 12% of children with respiratory allergies would benefit from compliance with more stringent ambient air quality standards in the northeastern part of the USA.

In conclusion, birth cohort studies such as the MAAS can provide new information on the natural history of allergic disorders such as CRC. In view of the biological diversities and complex gene-environment relationships in different populations, it is auspicial that the new Seventh Framework Programme for Research of the European Union provides the opportunity for an extension of such studies all over Europe.

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